DOCUMENT RESUME

ED 214 634 PS 012 717

AUTHOR Prensky, Arthur L.
TITLE Handicaps and Developmental Disabilities. Matrix No. 10.
INSTITUTION Administration for Children, Youth, and Families (DHHS), Washington, D.C.
PUB DATE Jan 82
NOTE 28p.; Paper presented at the Research Forum on Children and Youth (Washington, DC, May 18-19, 1981). For related documents, see ED 213 518-526, PS 012 713-715, PS 012 718, and PS 012 722-725.
AVAILABLE FROM Administration for Children, Youth, and Families, P.O. Box 1182, Washington, DC 20013 (no price quoted).

EDRS PRICE MF01/PC02 Plus Postage.
DESCRIPTORS *Autism; *Cerebral Palsy; Clinical Diagnosis; *Developmental Disabilities; Disease Incidence; *Epilepsy; High Risk Persons; *Learning Disabilities; *Mental Retardation; Research Needs; Therapy

ABSTRACT

This paper summarizes the recent advances achieved by research in the area of developmental disabilities, and discusses directions for future research in this area. Approximately 8 to 10 per cent of the pediatric population suffers from one or more developmental disabilities. The most common of these are learning disabilities, which include some behavioral problems, such as attention deficit disorders. Cerebral palsy, mental retardation, epilepsy, and autism are other disabilities that occur frequently in the pediatric population. Recently, there have been remarkable advances in understanding the cause of some developmental disabilities, notably epilepsy, mental retardation, and cerebral palsy. However, knowledge about other disabilities, such as learning disabilities and autism, is still very limited. Future progress in the diagnosis and treatment of developmental disabilities depends upon (1) an increased understanding of the causes of this disorder; (2) prevention of the occurrence or a decrease in the severity of developmental disabilities by treatment of their causes; (3) an increased understanding of the pathophysiology of the symptoms and signs that constitute a developmental disability; and (4) a realization that, in many instances, the symptoms and signs themselves can be treated by understanding their pathophysiology and without reference to their etiology. (Author/MP)

****
* Reproductions supplied by EDRS are the best that can be made *
* from the original document. *
****

ED214634

U.S. DEPARTMENT OF EDUCATION
NATIONAL INSTITUTE OF EDUCATION
EDUCATIONAL RESOURCES INFORMATION CENTER (ERIC)

X This document has been reproduced as received from the person or organization originating it.

☐ Minor changes have been made to improve reproduction quality.

• Points of view or opinions stated in this document do not necessarily represent official NIE position or policy.

MATRIX NO. 10

HANDICAPS AND DEVELOPMENTAL DISABILITIES

by

Arthur L. Prensky, M.D.
The Allen P. and Josephine B. Green
Professor of Pediatric Neurology
Washington University School of Medicine

PS012717

PAPERS
PRESENTED AT
THE RESEARCH FORUM
ON
CHILDREN AND YOUTH

May 18-19, 1981

Convened in Washington, D.C.

Sponsored by

Federal Interagency Panel on Early Childhood Research and Development

Federal Interagency Panel for Research and Development on Adolescence

Publication Date: January 1982

Research, Demonstration and Evaluation Division
Administration for Children, Youth and Families
Office of Human Development Services
U.S. Department of Health and Human Services

Papers available from: ACYF
P.O. Box 1182
Washington, DC 20013

HANDICAPS AND DEVELOPMENTAL DISABILITIES

Developmental disabilities such as cerebral palsy, mental retardation, learning disabilities and autism make up the majority of neurological problems seen in infancy and childhood. The prevalence of learning handicaps per 1,000 children is conservatively estimated at 75;[1] cerebral palsy between 4 and 5;[2] mental retardation with intelligence quotients of under 50 at about 3;[3] and infantile autism at 0.5 per thousand.[4] It must be stressed that terms such as "cerebral palsy," "mental retardation," "infantile autism" and "epilepsy" are used as diagnoses, but they really describe a constellation of symptoms and signs and not a disease. These handicaps result from many diseases, some of which are known and others that are yet to be described.

In each of the developmental disabilities that we have enumerated, recent advances in care and the need for future research to improve that care may be described as follows: (1) an increased understanding of the causes and pathophysiology that result in these symptoms and signs; (2) prevention of the occurrence or a decrease in the severity of developmental disabilities by treatment of their causes; (3) treatment of the symptoms and signs themselves without reference to their etiology.

Cerebral Palsy

A. Recent Advances

For the purpose of this discussion, we will accept the definition of cerebral palsy as "a disorder of movement and posture due to a defect or a lesion of the immature brain."[5] The incidence of epilepsy, mental retardation and learning disabilities is higher in children who have cerebral palsy, but these symptoms do not form an essential part of the definition of the disorder. The most common motor manifestations of cerebral palsy are abnormalities of tone, which either can be decreased (hypotonia) or increased (hypertonia or spasticity). Changes in tone generally are associated with some weakness and with decreased dexterity in performing fine motor movements. Dystonia, athetosis and chorea may occur in some patients. Ataxia and tremor when making voluntary movements are less common signs of cerebral palsy.

A variety of insults that can occur during pregnancy and delivery are associated with a higher risk for cerebral palsy in the infant. Intrauterine insults such as viral infections, antepartum hemorrhage or toxemia have been identified as resulting in a probable increase in the incidence of this disorder. Many children who develop cerebral palsy, however, have a history of problems at or soon after birth. Risk factors at this time include prematurity or postmaturity, low birthweight for gestational age, perinatal trauma, perinatal hemorrhage, severe hyperbilirubinemia and repeated convulsions in the neonatal period.[6]

A major contribution to the understanding of the pathogenesis and prevention of cerebral palsy in children is that (a) in most instances, high risk factors occur at or near the time of delivery, and (b) the pathology of the brains of many children with cerebral palsy is consistent with their having been subject to a hypoxic-ischemic

insult. The description by Banker *et al.*[7] that periventricular leukomalacia was a common pathologic lesion in preterm infants with motor disabilities led to an examination of the fetal circulation, which indicated that the periventricular white matter in the preterm infant was a watershed area,[8] which had a tenuous blood supply. Lesions in term infants also have been more severe in watershed areas, such as those between the anterior and middle cerebral arteries. When hemiparesis is a part of the cerebral palsy syndrome, it often is associated with atrophy of one hemisphere, or with a large porencephalic cyst in the vascular distribution of one vessel supplying blood to that hemisphere, usually the middle cerebral artery. However, in many instances cerebral palsy is not clearly related to vascular disease and occurs in term infants who have not had obvious problems during pregnancy and delivery. Therefore, continued pathology and epidemiologic investigations of this population are apt to be fruitful in identifying new risk factors.

Major advances have been made in reducing the incidence of cerebral palsy by identifying high risk pregnancies, by the introduction of fetal monitoring to be sure that prolonged periods of hypoxia and/or hypotension do not occur, by instituting immediate resuscitation at the time of delivery, and by continuing care of compromised infants in high-risk neonatal intensive care units.[9, 10] Prompt treatment of associated metabolic derangements that may lead to seizures and further compromise of the infant's cerebral circulation and oxygen supply also have improved the management of the high-risk infant. Hypoglycemia, hypocalcemia, hypomagnesemia and hyperbilirubinemia can be recognized and treated prior to producing significant symptoms, and thus decrease the risk of the development of cerebral palsy in the compromised neonate. Unfortunately, because of the great success in reducing mortality by intensive perinatal care, the morbidity actually may have increased, and it is not clear that the incidence of cerebral palsy really has decreased, since many neonates who might have died survive to acquire the disorder.

Substantial advances have been made in predicting infant populations that are at risk for cerebral palsy or other developmental disabilities prospectively.[11] In this country, the major population study has been that of the collaborative perinatal project of the National Institute of Neurological and Communicative Disorders and Stroke.[12] An assumption exists that states that if those children who are at high risk for cerebral palsy are identified early, it might be possible to treat their symptoms early in life and diminish their severity. Recent experimental investigations into the plasticity of the nervous system, especially the visual system, indicate that environmental manipulation does have an effect on the structure of the developing nervous system.[13, 14] It has been shown in subprimates that when targets for developing axons are injured, these axons may enervate other areas. This observation, along with the observation that the sensory motor area acts as a unit, and that motor discharges are profoundly dependent upon sensory input,[15] forms a theoretical basis for the early treatment of cerebral palsy. Unfortunately, it has never been established that the motor cortex of the human infant can be modified significantly by early regulation of basic motor patterns[16] or by altering sensory input.[17]

Knowledge of the identity, number and interactions of neurotransmitters with one another through the investigation of the metabolism and localization of amines and

amino acids within limited areas of the nervous system has led to the empirical treatment of disorders of movement and posture with drugs designed to mimic neurotransmitter function or alter the levels of such neurotransmitters as GABA, dopamine, norepinephrine or acetylcholine. No drug or combination of drugs has been entirely successful in relieving a motor disability in dosages that do not produce significant, deleterious side effects.[18] Methods of surgically treating the disabilities of cerebral palsy also have been developed. These include thalmotomy for dystonia and athetosis, and chronic cerebellar stimulation for disorders of tone and movement. Recent double-blind evaluations of the latter surgical procedure suggest that it may not achieve its purpose.[19] However, a better understanding of the interrelationships of motor pathways within the central nervous system may lead to improved surgical techniques for controlling the symptoms of cerebral palsy.

B. Research Goals

1. Continuing investigation of the biochemical basis of the development of normal movement directed at identifying the factors that control interrelationships between neurotransmitters at the synapse; the ways in which drugs may mimic or modify the effects of putative neurotransmitters; and the development and testing of new drugs that will be more effective in relieving the symptoms of cerebral palsy with minimal side effects. Such studies first need to be undertaken in suitable animal models and later the information applied to the study of children with cerebral palsy.

2. Further study into the physiologic interrelationships of neuronal populations, emphasizing the potential of these interrelationships to influence movement disorders. Animal models need to be used to better define the interrelationship between motor pathways in the damaged nervous system and whether ablation or stimulation of one pathway can ameliorate the effects of injury in another. In particular, the effects of sensory stimulation on the structure and function of the damaged motor cortex needs to be evaluated in animal models.

Studies of the plasticity of the developing nervous system at all levels of cellular organization and organ function need to be encouraged, using animal models with defined lesions.

Further clinical studies are needed: (a) to correlate the incidence and prevalence of nonprogressive movement disorders with etiology (if possible, the type of movement disorder should be related to cause); (b) to develop new methods to reduce the incidence of intrauterine infection, perinatal hemorrhage and hypoxicischemic disease; (c) to establish what other parameters of change in the intrauterine environment create an increased risk for cerebral palsy; (d) to develop more sophisticated tools for the measurement of the severity and the rate of change of a movement abnormality during therapy.

Current methods of treatment, including physical, occupational, drug, electrical and neurosurgical procedures, should be evaluated on a double-blind basis. Relatively homogeneous populations of children need to be identified for these trials. Therefore, accurate methods have to be developed to identify these populations in infancy or very early childhood when intervention should potentially be most effective.

Even if methods of early diagnosis of specific groups of children are successful, several problems exist before the effects of early treatment can be assessed adequately. First, children with motor deficits are more likely to suffer from other disabilities, such as psychomotor retardation or epilepsy, which may be difficult to diagnose in infancy. Second, any treatment requires a control population who would not have the benefit of a specific intervention in order to account for the effects of normal development. Yet, ethically, some form of habilitation will have to be provided for these children. The form of habilitation supplied to the control population must be sufficiently different from that given to the study population to assure the validity of the investigation. Third, we are evaluating complex aspects of human development over time, not just an isolated physical finding. For example, a drug or a series of therapeutic maneuvers may improve tone or sitting posture, but does that mean it has improved mental function or emotional control? Perhaps it has had the opposite effect. It will not be sufficient to limit the study of a treatment modality to effects on motor control. This means that a team of professionals will need to cooperate in designing and evaluating longitudinal studies during development. Physicians, psychologists, educators, social scientists, therapists, physiologists and biostatisticians will have to increase the coordination of their efforts in each treatment study. This kind of cooperation has been rare in the past, but must be a requirement for future research involving the care of disabled infants and children during development. The theoretical basis of many of these treatments has been established, but their applicability to the human neonate and developing infant and child has not been proven because of the difficulties recounted above. It is essential that the problems be recognized and overcome so that treatment programs that have been proven successful can be used to care for children with cerebral palsy.

Mental Retardation

A. Recent Advances

The definition of mental retardation we shall use is "Mental retardation refers to significantly subaverage general intellectual functioning existing concurrently with deficits in adaptive behavior, and manifested during the developmental period."[20] The etiology of mental retardation may be broadly divided into three subcategories: (1) Destructive brain lesions that occur *in utero* or at about the time of delivery. (In general, the same risk factors discussed under the heading of cerebral palsy also are associated with a higher incidence of mental retardation.) In addition, mental retardation can result from hemorrhagic or inflammatory lesions that cause progressive hydrocephalus, or retardation may be associated with chromosomal abnormalities or problems in morphogenesis of unknown cause. (2) Disorders that are associated with inherited metabolic diseases. (3) Disorders that are the result of abnormal endocrine function during pregnancy or in the neonatal period, such as hypothyroidism or hyper- or hypoglycemia.

In recent decades, there have been major advances in defining the specific causes for an individual's psychomotor retardation. Techniques for analyzing the accumulation of substrates, such as amino acids, organic acids, fatty acids, lipids, mucopolysaccharides or sugars, have become highly sophisticated.[21] In many instances, unknown

substrates can be identified by mass spectrometry within a matter of hours to days, rather than weeks to months as in the past. In those disorders where substrates accumulate or are excreted in excess quantities, it often has been possible to establish which enzyme is deficient and to what degree.[22, 23] Fundamental biochemical research that established the concept of isoenzymes that act under different conditions, often in different tissues, has been seminal to understanding the metabolic basis of many of these inherited disorders.[24] Similar dramatic advances have been made in the field of chromosome analysis. Banding techniques have made it easier to establish the existence of deletions, reversals or improper transfer of genetic material within a chromosome or from one chromosome to another. This has resulted in a proliferation of chromosomal disorders in which retarded children with dysmorphic features have been shown to have too much or too little genetic material.[25] Recently, families of retarded males, who usually have no dysmorphic features, have been shown to have an anomaly of the X chromosome when the cells are grown in a folate-deficient media.[26]

A technology has been developed that makes it economically feasible to apply the advances made in the diagnosis of causes of mental retardation to a large population. Thus, screening for phenylketonuria is now mandatory throughout most of the United States. Screening for other amino acid disorders also is possible, as is screening for the storage of galactose early in infancy, and for such endocrine disorders as hypothyroidism.[27] Culture techniques for fibroblasts, amniotic cells and white blood cells have become standardized and relatively inexpensive, making it possible to perform enzymatic or chromosomal analyses on small numbers of an individual's cells grown in culture. These types of analyses allow for early identification of patients suspected of having an inherited metabolic disease (such identification, in many instances, may be made *in utero*), and for the identification of carriers.[28, 29]

There remains the large number of retarded patients whose symptoms have no known cause. Some of these patients have brains that appear to be grossly normal, while others have obvious developmental abnormalities such as hydrocephalus, lissencephaly, or polymicrogyria. The recognition that intrauterine viral infections can produce developmental as well as destructive lesions of the nervous system has been a major landmark in understanding the possible cause of retardation in some children who are born with major brain anomalies. The production of hydrocephalus *in utero* by mumps and other viruses in experimental animals, as well as the production of cerebellar dysgenesis by an intrauterine viral infection, have been major discoveries.[30] Awareness that, even when the brain appears to be grossly normal, abnormalities in the microscopic structure of the neurons, particularly of the dendritic spines and their synapses, may be associated with mental retardation is another landmark in the investigation of the pathogenesis of retardation.[31]

The recognition that intrauterine and extrauterine disturbances may summate to produce profound disturbances in brain growth and function, when a single insult produces considerably less of a disturbance, has to be considered potentially important in understanding the environmental contribution to some retardation syndromes.

When the causes of mental retardation can be identified, they often can be prevented or treated. Prevention involves identification of the fetus who has a disease *in utero* by enzymatic or chromosomal analysis and termination of the pregnancy, if that is the family's desire. In many families in which the fetus is known to be at risk, this determination can be made at the end of the first trimester of pregnancy with a very high degree of accuracy.

Other disorders can now be treated. For example, phenylketonuria, maple syrup urine disease and other amino acidurias, which involve the accumulation of ammonia or organic acids, such as methylmalonic acid, can be treated by withholding substrate[32] or, in certain instances, by the addition of pharmacologic amounts of co-factors such as vitamin B_6 or B_{12};[33] hypothyroidism can be treated by replacement of the hormone. If these therapies are instituted early in postnatal life, the incidence of retardation from these causes drops markedly.[34] Similarly, the prevention of severe hydrocephalus, either by repeated lumbar punctures, the use of dehydrating agents such as glycerol, or shunting cerebrospinal fluid to the heart or abdominal cavity, has resulted in improved intellectual functioning in that population of infants and young children in which the hydrocephalus is the result of obstruction of the flow of cerebrospinal fluid rather than destruction of brain tissue. Mental retardation that is the result of external insults, such as those enumerated in the section on cerebral palsy, or caused by poor fetal or infant nutrition, also can be prevented in whole or in part by early treatment.

The treatment of mental retardation as a symptom involves a positive approach toward the education of these individuals. Perhaps the most significant advance in this area is the realization that even the most profoundly retarded can be trained to some degree by extending the techniques of operant conditioning to modify behavior and to teach these children to perform some of the simple tasks needed for everyday living.[35]

B. Research Goals

Further research needs in the field of mental retardation are many. Valid animal models should be developed that can be used to study the putative causes of mental retardation by appropriate anatomic, physiologic and biochemical techniques. This means that attempts have to be made not only to standardize cognitive tests used in animal models and correlate these tests with alterations in physiologic, anatomic and biochemical parameters in the brain, but also to develop methods by which psychological tests validated in animal models will have some meaning in terms of human psychometric function in disease.

It also is important to continue to study the effects of manipulation of the environment in animal models, i.e., nutrition, overcrowding, sensory stimulation and deprivation, etcetera, to better define the pattern of impaired function in later life, correlating these environmental insults with anatomic physiologic and biochemical factors in brain development. The effects of multiple insults should be studied, since this is apt to occur in economically and socially deprived human populations. Studies of the effects of reversal of such insults should be emphasized.

It is important to continue research into the prevention of mental retardation in humans by continuing to define specific causes. Epidemiologic studies, therefore, are necessary to establish the size of the population in which the cause of this symptom remains unknown and to search for new clues about etiology. Studies are needed to define the chances that a family will have a second retarded child if their first child is retarded and has no known inherited metabolic or degenerative disease. Longitudinal studies of the development of populations at greater risk for psychomotor retardation, such as the preterm infant are in progress,[36] and further investigations need to be encouraged.

Where causes are known, it is important to continue research into treatment. For example, continued exploration is desirable of techniques for the introduction of enzymes into the nervous system and other organs to treat lipid and mucopolysaccharide storage diseases. We know that certain disorders can be improved by the use of co-factors, particularly vitamins. Do other substances which act as co-factors for enzymes, such as trace metals, have a similar beneficial effect with some subpopulations of children with inherited mental retardation caused by a metabolic disorder?

It is important to continue investigation of the environmental influences that may result in retardation, both *in utero,* i.e., maternal nutrition, placental function, and contact with toxic substances, and in extrauterine life, i.e., the effects of adequate postnatal nutrition. Early correction of minor sensory impairments, use of increased sensory stimulation and the greater use of behavior modification programs to stimulate learning or to improve behavior, beginning in preschool years, should be emphasized.

Investigations should be undertaken to look systematically for endocrine and neurotransmitter abnormalities in populations of retarded children with the hope of finding more specific modes of therapy to improve behavior and motivation.

Learning Disabilities

A. Recent Advances

Learning disabilities are a heterogeneous group of disorders and may be defined in two ways. The first definition concerns those people who, despite normal intelligence, are unable to acquire one or more selected school skills at a normal rate. For a variety of reasons, such individuals have difficulty with either reading, writing, mathematics, or spelling. These individuals are said to have a specific learning disability. A broader definition of learning disabilities involves people of normal or borderline intelligence who are unable to learn at a rate consistent with expectations based upon their intelligence quotient. This inability to learn may be caused by problems with behavior, particularly with attention, as well as with an inability to grasp concepts or learn specific skills. Such children may have deviations that become manifest by various combinations of impairment, of perception, conceptualization, language function, memory and control of attention, impulse or motor function.[37]

The causes of learning disabilities, be they specific or general, are poorly understood. There is certainly a higher incidence of learning disabled individuals in certain

families. It is not clear, however, whether genetic variations, biochemical irregularities or insults to the brain during development are responsible for these extremely common and serious problems. The majority of these children have not been subjected to recognizable stresses during pregnancy or birth. Endogenous or exogenous insults, other than those commonly seen with cerebral palsy or mental retardation, are probably etiologically related to the majority of children who have a learning disability. Perhaps the major clue to the *type* of insult that may be looked for in the future has been the observation that chronically elevated serum lead levels, insufficient to produce overt neurologic disease, may be associated later in life with deficits in attention and in learning.[38]

Despite a lack of specific etiologic causes for learning disabilities, the neural substrate of these disorders has been investigated actively in recent decades. It has been recognized that directed attention is fundamental to appropriate behavior and to learning. The physiological mechanism by which groups of brain cells act in concert to direct attention has been investigated, with considerable information derived about the way in which cells in the association cortex filter sensory input and control motor responses to that input.[39]

The biochemical basis of attention and behavior also has been investigated carefully and the relationship of central noradrenergic and dopaminergic synapses to behavior have been partially elucidated.[40] It is clear, however, that there are other substances apart from putative neurotransmitters that regulate the individual's ability to respond to external stimuli. Intrinsic brain peptides probably exert a neuroregulatory effect. Thus, the biochemical pharmacology of enkephalins, beta-endorphins, substance P, vasoactive intestinal polypeptide and other such substances clearly are going to be important in the study of attention and behavior in the future, as is the interrelationship between the production of hormones and brain function.

This purely biochemical approach to activity and attention has been challenged repeatedly.[41] This challenge stresses the fact that a child's behaviors are to a great degree controlled by the demands of his environment. Hyperactivity, and by implication attention deficits, are felt to be best approached using biopsychosocial models in which the child's interaction with the home and school environment is considered at least equally with his constitutional makeup. Long-term follow-up studies of hyperactive children suggest they remain impulsive and fail to develop good social skills or work habits. It is not clear from the few studies of older hyperactive children that have been undertaken whether treatment of this disability (a) needs to be continued into adolescence or even adulthood, (b) is effective in modifying adolescent behaviors if begun early in childhood, and (c) can be instituted for the first time in adolescence with any benefit to the child.

The concept that there are critical periods in the development of behavior is an exceedingly important one, especially when linked to the observation that the behaviors that develop during such periods in mammals or birds may be regulated by endogeneously produced substances, such as hormones, as well as by manipulation of the external environment.[42, 43]

Few, if any, remarkable advances have been made in the treatment of learning disabilities such as a developmental dyslexia or general disabilities resulting from

behavioral problems or lack of attention. Perhaps the greatest step forward has been the widespread recognition that these syndromes exist, that they represent a medical disability, and that the children who suffer from them require special help. Many of the procedures suggested for helping children with learning disabilities have not received wide acceptance in the medical community and are extremely controversial. This includes the use of stimulants or other drugs that will alter the level of neurotransmitters in brain, the reduction of sugar and the removal of additives from the diet, and the application of behavior modification techniques in the school situation. Of the three approaches, the latter may be the least controversial, since it is quite possible that drug therapy, in part, is effective because it readjusts the attitudes of parents and teachers.[44] Several controlled studies have failed to demonstrate clearly that a diet deficient in glucose and food additives increases attention appreciably,[45] or that a small group of favorable responders to diet therapy was affected adversely by adding artificial colorings to their diet.[46]

There is a group of children whose attention and behavior are reasonably good, but who have difficulty processing information either by the visual or auditory route. It has been possible to achieve some degree of success with these children by teaching them the information they need to know to be effective citizens by alternative methods. For example, poor auditory readers may be able to memorize what words look like and develop a sufficient reading vocabulary, remembering and using the information when it is presented in that manner. Children who cannot manipulate numbers on paper may be able to do so with the use of a calculator. Innovative use of electronic equipment is becoming recognized as a teaching method for treating the symptoms of a learning disability and reducing the functional impairment they cause.

B. Research Goals

Research into learning disabilities in the future depends upon better defining the causes of these disabilities. Specific syndromes need to be defined and epidemiologic studies done to estimate their prevalence and incidence and to identify associated risk factors. The possible genetic basis for such syndromes needs to be better established.

Attempts need to be made to develop valid animal models for disorders of attention and emotional lability which may interfere with learning. This, in turn, means that psychological tests have to be devised for animals that have some validity when compared to standardized tests in humans. The development of such animal models is a necessary prerequisite to understanding alterations in regional neurochemical and physiological function that may underlie disorders of attention and behavior. Such models also can be used to further elucidate the types of insults that may alter learning and behavior, the period at which the organism is most susceptible to those insults, and the biochemical basis for that susceptibility.

Irrespective of whether such models can be developed in animals, it is important to continue the investigation of the neurophysiological and neurochemical substrates that control normal animal behavior during development and in adult life. It is

particularly important to clarify further the neurophysiologic mechanisms that underlie the organism's ability to attend to a specific stimulus while eliminating extraneous ones.

There is a need to characterize further specific syndromes that make up the heterogeneous population of learning disabilities in children. The development of test procedures that will best identify these syndromes, and, if possible, predict them, must receive a high priority.

It is extremely important to define whether or not there are critical periods for the development of behavior and learning in humans and, if so, during what stage in development they occur, how they are regulated, how long they last and whether or not the time at which they occur and their duration can be modified by external agents.

The treatment of symptoms needs to be improved. Research is needed to provide adequate information concerning the indications for drug treatment of children with learning disabilities, the length of time these drugs should be administered, their long-term effects, and how to predict which drugs may be best for an individual child. In addition, the development of new drugs and their testing need to be encouraged. The mechanisms by which these drugs modify behavior should be studied in human populations by studies of the turnover of neurotransmitters, levels of neuroregulators, and neuroendocrine function.

Populations of children with specific syndromes need to be studied, in order to determine if exposure to organic or metallic substances in the environment at low levels affects learning.

It is important to evaluate, in well-defined groups of children with learning problems, whether practices currently used in special education enhance the capacity of these children to learn. If at all possible, such studies should be controlled.

Infantile Autism

A. Recent Advances

Autism will be described as a symptom complex in which children have (a) a delay in language development and abnormal speech characterized by bizarre sounds, echolalia and jargon; (b) a lack of interest in other human beings with poor eye contact, limited emotional attachments and an appearance of aloofness; and (c) a marked resistance to change in the environment (although unexpected changes that ordinarily elicit a startle in normal infants and children frequently fail to do so in the child with autism). These children also may have periods of hyperactivity or hypoactivity and a short attention span. They often exhibit a relative insensitivity to pain. Rutter noted that such children do better when given tests of visual spatial function or rote memory than they do with language or the processing of symbolic or sequenced information. He felt a cognitive defect may be the primary handicap in this disorder.[47]

The etiology of autism is unknown. There is no distinctive pathology described as yet, although some have noted that the analysis of CT scans suggests that the dominant speech area may be smaller with an enlarged left temporal horn when compared to controls of the same age.[48] Situations that put the fetus or infant at risk to develop early infantile autism (in the absence of mental retardation) have not been described.

The investigation of the pathophysiology of autism thus far has not yielded particular benefits with regard to the nature of the syndrome, its causes or its treatment, though these studies tend to reinforce the idea that infantile autism is an organic disorder.[49] Physiological investigations have indicated a failure of sensory motor integration and inadequate galvanic skin responses to auditory and visual stimuli in autistic children, consistent with the observation that these children do not show an adequate startle response. Vestibular nystagmus appears to be suppressed in many autistic children. The rapid eye movement activity of the REM phase of sleep also is decreased in infantile autism. Many of these responses resemble those seen in normal infants at a younger age, suggesting a delay in maturation due to unknown causes.[50]

A second line of research involves the metabolism of indoles in peripheral blood, blood platelets, and most recently, in the cerebrospinal fluid. It also is possible that there are abnormalities in brain dopamine and norepinephrine metabolism. However, no consistent biochemical abnormality has yet been found.[51]

The treatment of the syndrome has proven to be as difficult as defining its causes. Megavitamin therapy, particularly with pharmacologic doses of B_6 has been advocated,[52] but the results have not been consistent nor the studies designed to be clearly double-blind and prospective. The same may be said for the use of L-dopa in the treatment of this disorder. Educational therapy oriented toward a highly structured approach, using behavior modification techniques, has proved to have some effect among a subgroup of autistic children.

B. Research Goals

1. Epidemiologic studies of the disorder to ascertain incidence, prevalence, and risk factors. These studies should include detailed histories concerning pregnancy, birth, and the neonatal period, to attempt to define early injuries that might interfere with normal brain maturation.

2. Continued physiologic, psychologic, genetic and biochemical studies to determine the cause of autism. Objective measures, which do not require cooperation on the part of the patient, designed to test the child's ability to integrate different modalities of sensory stimuli should be developed.

3. Evaluation of the pathology of the brains of autistic children, including use of the Golgi technique.

4. Expansion of long-term prospective controlled studies on the efficacy of various treatment methods.

5. Attempts to develop animal models for segments of the syndrome (it will probably be impossible to produce a model of the entire syndrome of infantile autism),

in order that the developmental anatomy and regional biochemistry of these animals can be evaluated and perhaps lead to a better understanding of the syndrome in the human population.

Epilepsy

Epilepsy will be defined as two or more seizures occurring without fever and in the absence of an acute insult to brain, such as trauma, infection, or a serious metabolic disorder such as hypoglycemia. Where specific types of epileptic seizures are discussed, we will use the International Classification whenever possible.[53]

TABLE 1

Traditional Classification	International Classification
A. Generalized Seizures Generalized seizures are bilaterally symmetrical without local onset. 1. Petit Mal 2. Grand Mal (tonic, clonic, or tonic-clonic)	A. Generalized Seizures Generalized seizures are bilaterally symmetrical without local onset. 1. Absence seizures 2. Tonic-clonic seizures 3. Clonic seizures 4. Tonic seizures
B. Unclassified Disorders 1. Myoclonus 2. Atonic seizures 3. Akinetic seizures 4. Infantile spasms	5. Myoclonus 6. Atonic seizures 7. Akinetic seizures 8. Infantile spasms
C. Focal Motor or Jacksonian Seizures	B. Partial Seizures (seizures beginning locally)
D. Temporal Lobe or Psychomotor Seizures	1. With elementary or simple symptomatology (generally without impaired consciousness) a. Motor symptoms b. Sensory symptoms c. Autonomic symptoms d. Compound forms
	2. Temporal Lobe or Psychomotor Seizures with Complex Symptomatology (generally with impairment of consciousness) a. Impairment of consciousness only b. Cognitive symptoms c. Effective symptoms d. Psychosensory symptoms e. Psychomotor automatisms f. Compound forms
	3. Partial Seizures that become secondarily generalized

The prevalence of epilepsy in the entire population of the United States is approximately 5 to 6.5 per 1,000 people.[54] However, seizures are more common in children, and in the first 5 years[54, 55, 56] of life the incidence of convulsions is estimated to range between 2% and 6%, the majority being febrile seizures. While prevalence and incidence vary widely from one study to another, epilepsy is a childhood disorder, because about 75% of all epileptics develop their symptoms prior to 21 years of age.[57]

A. Recent Advances

In the past decade, primarily because of the excellent statistics gathered in the collaborative perinatal project of the NINCDS, it has been possible to better define the symptoms and consequences of febrile seizures as compared to epilepsy. It always had been recognized that there were families that had a tendency to have seizures with fever during infancy and early childhood. However, these were thought to be generalized and brief; when prolonged or focal, such seizures frequently were diagnosed as epilepsy, even though they occurred with fever in children who were otherwise perfectly normal. Thanks to the excellent epidemiologic investigations resulting from the perinatal study, we now know that these complex febrile seizures are not associated with a significantly higher incidence of epilepsy later in life, unless the patients already have other signs of neurologic damage or there is a family history of epileptic seizures.[58] The distinction has saved many children from being treated unnecessarily and many families from years of concern that their child might be an epileptic. This evaluation of febrile seizures should serve as a model for needed future epidemiologic studies concerning the prognosis of specific seizure subtypes. Perhaps it is necessary to follow the life histories of patients with epilepsy more than the children with any other developmental disability, because over the centuries, epilepsy, which often is benign, has been considered a catastrophic and permanently disabling illness. There are now two excellent studies that indicate that seizures cease in a proportion of childhood epileptics as the brain develops.[59, 60]

Further investigations are necessary to better define which populations of epileptic children have the best prognosis, whether there is any difference in their life span compared with that of the normal child before or after puberty, whether they continue to be at greater risk for injury while performing tasks required in an industrial society, and whether the intelligence of epileptic children remains stable over the years and is commensurate with their educational achievement. Epidemiologic information remains a necessary prerequisite for many of the clinical studies that should be undertaken on populations of epileptic children in the next decade.

The biochemistry and physiology of epilepsy and its effects on the developing brain have been described much more clearly in recent years. Study of the neurochemistry and neurophysiology of epileptic discharges has been advanced by the use of several kinds of animal models. One strain of mice has a hereditary susceptibility to audiogenically induced seizures. Generalized seizures also can be provoked by electroshock or the use of drugs administered systemically, such as strychnine or pentylenetetrazol.[61] Focal seizures have been produced by direct application of drugs to brain, notably penicillin[62] and cobalt. Topical application of acetylcholine to the cortical surface also produces focal seizure activity.

While excitatory neurotransmitters, such as acetylcholine and glutamic acid and chemicals that deplete the brain of an inhibitory neurotransmitter, gamma amino butyric acid, can produce seizures, the exact mechanism is known by which these biochemical alterations produce neuronal depolarization and repetitive firing of nerve cells. Energy is required for the maintenance of an electrochemically stable cell membrane, and drugs that interfere with energy metabolism or with membrane transport of sodium and potassium will result in a cell that is more likely to produce an epileptic discharge.[63] This, in turn, may be affected by cyclic nucleotide levels in different brain areas.[64] A number of direct and indirect methods are available now to measure energy metabolism in relation to a seizure. One of the major discoveries of the last decade has been that 2-deoxyglucose will be taken up at a rate proportional to the use of glucose in a brain area, but is not further metabolized. Therefore, radio-labelled 2-deoxyglucose can serve as a measure of glucose utilization in animal models.[65] It also is possible to freeze brains rapidly and measure levels of high energy phosphate compounds directly.[66] In the human, both cerebral blood flow, glucose utilization and depletion of high energy phosphates during an epileptic discharge can be measured by the use of positron emission tomography[67] and nuclear magnetic resonance. There is no doubt that these techniques will be improved in the next decade to make more precise measurements possible in children with various kinds of seizure disorders.

Studies of developing animals make it clear that without artificial respiration during a sustained seizure, the brain incurs a severe oxygen and energy debt and acidosis occurs.[68] Even with artificial ventilation, the brain cannot sustain its normal rate of DNA, and protein synthesis and seizures during development may result in permanent damage.[69] There is little reason to believe that these biochemical changes, which have been elucidated in animal models, are not applicable to humans.[70]

Knowledge of the neurophysiologic substrate of epileptic seizures also has been expanded in the last decade. Normal neuronal function is basic to the understanding of the seizure mechanism. It long has been known that the neuronal membrane is not impermeable to sodium, potassium and chloride, and that while they are distributed unequally in the intra- and extracellular spaces, they can move across the cell membrane. It is known now that excitatory neurotransmitters directly affect the flux of both sodium and potassium, resulting in depolarization of the membrane, while inhibitory neurotransmitters stabilize the membrane by increasing the selective permeability to chloride. It still is not clear how the interaction of inhibitory and excitatory postsynaptic potentials occurs on the surface of a single cell membrane to permit or inhibit the cell's discharge. Apparently the potentials of many synapses summate, resulting in excitation that overcomes the protective hyperpolarizing action of the cell that follows a single discharge. The cell then begins to fire at an abnormally high frequency. These oscillations are recurring depolarizations and, when they occur in many cells at the same time, they reflect on the surface of the brain as a spike. An epileptic seizure, therefore, represents the oscillations of depolarized membranes of many thousands of cells. Seizure termination is associated with hyperpolarization which may be caused by the actions of a sodium pump and, in part, from the removal of extracellular potassium from the area of excitation by glial cells.[71]

The basic neurophysiology of the epileptic cortex needs a great deal of further study. The mechanisms that have been described are simple ones, and in order to understand the effect of antiepileptic drugs in preventing focal seizure discharges and their spread to other cells, a great deal more must be learned about the surface membrane of the neuron, its response to putative neurotransmitters, and the control of the ionic environment of the cell in relation to the summation of excitatory postsynaptic potentials. There is every reason to expect that fundamental investigations of membrane neurophysiology and cell neurochemistry eventually will further our ability to control epilepsy.

Even more striking advances have been made in the diagnosis and treatment of epilepsy over the last decade, and these may be expected to continue in the future. Epilepsy is a symptom that is diagnosed by evaluating the patient's history. The electrical evaluation of brain activity (the electroencephalogram, or EEG) only assists the physician in making the diagnosis of an epileptic seizure. The EEG, however, can be very helpful to correlate unusual symptoms and signs with disturbed cortical electrical function. Extended recordings, with or without concurrent television monitoring of the patient, can aid in this correlation. Such recordings may be made on tape or on regular EEG paper. The information is transferred to a computer capable of analyzing the frequency of paroxysmal transients during a specific time interval. Extended EEG recordings with monitoring of the patient's behaviors by television have proved useful in defining the clinical repertoire seen with petit mal seizure disorders[72] in the treatment of intractable epilepsy[73] and in identifying patients whose unusual paroxysmal movements may not be epileptic (possible pseudoseizures).[74]

While it is unusual for epileptic seizures to occur in children as the result of a tumor or vascular malformation without the presence of other symptoms and signs of neurologic disease, some children with focal seizures do have silent lesions, especially in the frontal or temporal lobes, that now can be identified easily and safely, using computerized tomography.[75, 76]

There are three important methods of treating epileptic seizures: the use of anticonvulsant drugs, the ketogenic diet, and surgical procedures to reduce or eliminate seizures. During the last decade, three major drugs have been added to our armamentarium for the treatment of seizures in children -- clonazepam, which is effective primarily against myoclonic, atonic and akinetic seizures; carbamazepine, which is effective against partial seizures with either simple or complex symptomatology; and sodium valproate, which is effective against a wide range of generalized seizures, but is particularly useful in treating infantile spasms, massive infantile myoclonus, akinetic seizures and petit mal. Our understanding of the pharmacokinetics of these drugs is incomplete, and we know very little about how they or any other antiepileptic medicine works in the nervous system at the cellular level.[77] There is no doubt, however, that these drugs, taken singly or in combination, have made it possible to obtain satisfactory control of seizures in a number of children who were hitherto considered hopeless. Sodium valproate is a drug that is of particular interest because it is a branched-chain fatty acid, unlike all other drugs now in use for control of epilepsy. It therefore introduces the concept that antiepileptic drugs may

not need to have a barbituric acid or other ring structure in order to be effective. The biopharmacology of these medications needs to be better understood. In fact, much more work needs to be done to understand the biokinetics of drugs that have been in use for much longer periods of time, such as phenytoin.[78] The toxic effects of antiepileptic medications when used in pregnancy only recently have been described, and the magnitude of the danger has yet to be estimated accurately.[79]

The ketogenic diet is not a new form of therapy; it was introduced in the 1920s. It has been resurrected in recent years, however, with considerable success in the treatment of atonic, akinetic and myoclonic seizures. Once again, as is the case with many new and old antiepileptic drugs, the mechanism of action of the ketogenic diet is not certain. It seems to be related, however, to the utilization of ketone bodies and ketoacids rather than glucose as energy sources by brain. Why this confers a protective effect is uncertain.[80] Prolonged use of the ketogenic diet creates problems that have yet to be evaluated thoroughly. It is known that the absorption of calcium and vitamin D is reduced, and that these substances must be supplemented in patients receiving the ketogenic diet for any length of time. The long-term cardiovascular effects of a high fat diet have not been well studied. Since the ketogenic diet is a valuable addition to the armamentarium of the physician treating the epileptic child, these matters require investigation over a period of years.

Major strides have been made in the surgical control of seizures. Basically, the surgical control of epilepsy still centers about removal of an identifiable seizure focus. Until recent years, however, such foci had to be identified clinically or by the scalp EEG. Neither method was highly successful in identifying either frontal or mesial-temporal foci that produce a great many focal seizures with or without secondary generalization. Seizures originating from these areas are often especially difficult to control. Advances in electrophysiology have been applied to the clinical identification of seizure foci. Depth electrodes now can be placed in the mesial-temporal cortex to identify electrical discharges associated with partial seizures with complex symptomatology.[81] Batteries of extradural electrodes can be placed for long periods of time and the patient's seizure activity recorded simultaneously with his EEG on a split-screen television monitor. It is possible therefore to see EEG changes in dural electrodes prior to the onset of a clinical seizure. This allows precise identification of the focus.[82]

It frequently is necessary to know whether the focus lies in an area that is *active*, (one that controls important language, movement or sensory functions). There is still no foolproof way of identifying whether a seizure focus in the dominant hemisphere in the posterior frontal, parietal or posterior temporal region is involved actively in language function. It is possible, however, by recording evoked responses from the cortical surface to identify the sensory motor area and the primary auditory and visual cortices. The technique allows the surgeon to evaluate whether an area of damaged epileptogenic cortex still is involved in important sensory motor functions, or serves as an auditory or visual receptive area. It is to be hoped that in the near future techniques will be devised to allow similar identification of areas that are essential for the processing of language and for conceptual speech.

Other surgical techniques have been advocated for control of epileptic seizures, but their effects are much less certain. Chronic cerebellar stimulation is thought to inhibit cortical seizure foci and lessen seizure activity, although recent studies suggest that this may not be the case.[83,84] Section of cerebral commissures, notably the corpus callosum, is felt to reduce the incidence of generalized seizures where a focus cannot be identified.[85] This type of surgery needs to be evaluated much more carefully in the next decade. It differs in principle from removal of an epileptic focus in that the object of the surgery is to prevent spread of the seizure activity and its generalization to the opposite hemisphere, while the object of removal of a seizure focus is to eliminate the source of the epileptic activity.

B. Research Goals

Over the next decade improved care of the child with epilepsy is going to depend upon research on many levels. We must improve our biochemical and physiological understanding of what happens to a single neuron and a population of neurons before, during and immediately after an epileptic discharge. The metabolic prerequisites for membrane depolarization, as well as the metabolic consequences of prolonged seizure activity, need to be clarified. Basic knowledge of this kind is a necessary prerequisite to our understanding of how drugs may work to abort epileptic seizures. It is also essential to have this type of information if we are to learn about the ways in which repeated or prolonged epileptic seizures diminish brain function in some children, and how to prevent those unfortunate results.

The development of new drugs for the treatment of epilepsy can evolve in three ways: serendipitously; by systematically altering the structure of existing drugs; and by developing drugs of new and unique structures based upon our knowledge of how existing drugs prevent the development or spread of seizure activity. No major drug has been developed by this last method of approach, even though it would appear to be the most logical. The reason for that is that we know almost nothing about how any of the major antiepileptic drugs affect cell function at a molecular level. It is extremely important that this research continue, in order to see whether there are common effects that are responsible for the success of different drugs that prevent seizure activity. In addition to animal models for testing drug effects on seizures and studying their biochemical effects on neuronal populations, it is now possible to evaluate these drugs in cell culture[86] and in isolated organ cultures, such as the hippocampus which has been transplanted to the anterior chamber of the eye.[87] It is also important that we better understand the effects of the ketogenic diet on neuronal metabolism and seizure prevention. Answering the question of why a nerve cell is more resistant to depolarization when metabolizing ketones and ketoacids instead of glucose may reveal basic information about the excitability of neuronal cell membranes.

While investigations are taking place at this level, more clinically oriented studies are needed to test the efficacy of new drugs and new surgical techniques. The toxic properties of drugs used to control seizures during pregnancy and in prematures and neonates should be investigated much more carefully and compared to the possible benefits of seizure control.

Control of epilepsy by surgical excision of brain tissue must be made as safe as possible. Many epileptic foci removed surgically exhibit changes that are consistent with a chronic encephalitic process,[88] although to the best of our knowledge, a virus never has been cultured or isolated from this tissue. Since this appears to be one of the common pathologic substrates of uncontrolled seizure activity, continued investigation is extremely important of patients with chronic uncontrollable partial seizures for a possible infectious cause of a low grade focal encephalitis.

Similarly, there are certain types of seizures, such as those seen in the Lennox-Gastaut syndrome and infantile spasms, that result in a high incidence of retardation in children who were normal prior to the onset of seizure activity. The source and cause of these seizure syndromes are unknown, and their strong association with mental retardation remains a mystery.[89] Techniques to investigate these problems, using the PET scanner or other noninvasive methods, should be given the highest priority, because so many of these children deteriorate mentally.

The general association of various types of seizure activity with psychomotor function, and particularly with the stability of psychomotor function over time, needs to be investigated prospectively. Does good seizure control improve psychomotor function or school performance over a period of years? It is true that many children with epilepsy do poorly in school, even though their psychometric functions are not significantly below normal. The relationship between school performance, psychometric performance and seizure activity needs to be studied. The psychosocial effects of epileptic seizures have been described but not quantitatively evaluated.[90] Methods of doing so need to be developed, in order to gain some insight into why many epileptic patients, who are not severely incapacitated, do not work.[91]

These are but a few of the problems that face the medical community if it wishes to reduce the incidence of seizures in American children and improve the adjustment of those who do develop epilepsy so that they may live normal lives.

Summary

Approximately 8% to 10% of the pediatric population suffers from one or more developmental disabilities. The most common of these are learning disabilities, which include some behavioral problems, such as attention deficit disorders. Cerebral palsy, mental retardation, epilepsy and autism are other disabilities that occur frequently in the pediatric population. While these terms are used as diagnoses, they actually refer to a constellation of symptoms and signs and not to a disease. Frequently, several of these disorders coexist in the same child, who may have both cerebral palsy, mental retardation and epilepsy, or epilepsy and a learning disability. The nature and severity of these disabilities vary from one individual to another. In fact, each child is unique. One of the major problems for clinical investigators working in the field of developmental disabilities is to define a population of children that is relatively homogeneous, while still accounting for individual variables, in order to evaluate the effects of treatment. In order to do this, the definition of subcategories of developmental disabilities has to be made more strict, and the description of test populations more precise.

In many instances, no cause is found for a developmental disability. In other instances, the end result may be an outcome of multiple causes, some genetically determined or the result of disorders during intrauterine development; and others, the result of external stresses superimposed upon the infant after birth. The ways in which multiple insults interact with one another to produce a deleterious effect on brain structure and function require further investigation in human populations and in animal models during the next decade. In addition, it is important to study how an advantageous extrauterine environment possibly may ameliorate the effects of genetically determined or intrauterine insults. The study of the effects of multiple insults almost certainly will make use of the concept of critical periods during development. These are limited periods of time during which negative stresses or positive reinforcements may be most potent in modifying the effects of a lesion.

Developmental handicaps result from many diseases that damage brain, but the symptoms and signs that they cause may be similar. It is possible that a symptom told to the physician – for example, a description of a partial seizure with complex symptomatology – or a sign he notices, such as spasticity, may have a common pathophysiology irrespective of the cause that brought on that symptom or sign.

Past advances in the diagnosis and treatment of developmental disabilities and, in all probability, future progress depend upon: (1) an increased understanding of the causes of this disorder; (2) prevention by treatment of causes; (3) an increased understanding of the pathophysiology of the symptoms and signs that constitute a developmental disability; and (4) realization that, in many instances, the symptoms and signs themselves can be treated by understanding their pathophysiology and without reference to their etiology.

Recently, there have been remarkable advances in understanding the course of some developmental disabilities, notably epilepsy, mental retardation and cerebral palsy. But our knowledge about others, such as learning disabilities and autism, is still very limited. Understanding the damaged brain, which is the source of a developmental disability, is dependent directly upon knowledge of normal brain development. Research into all aspects of normal brain development, such as neuroanatomy, neurophysiology and neurochemistry, must continue.

Much of our knowledge of the principles of normal brain development comes from the study of animal tissues. Furthermore, animal models are required to study many forms of brain damage, since it is possible to limit variables by restricting the extent or duration of a lesion in an animal and to structure their environment; whereas, lesions in humans are experiments of nature and thus haphazard. It is not clear, however, that an external injury inflicted upon an animal is a model for a genetic disease in the human, even if the biochemical or structural changes produced are similar. Much of the future work to be done in the field of developmental disabilities must be done on human populations that suffer from these disorders. Continued intensive epidemiologic investigation is needed of risk factors associated with cerebral palsy, mental retardation, epilepsy, and, in particular, with autism and learning disabilities. Future epidemiologic studies should emphasize the possible additive effects of multiple risk factors. It is to be expected that further advances in human genetics, especially those in the identification and analysis of chromosomal defects and in intermediary metabolism, will increase the number of treatable or preventable causes of developmental disabilities.

It is even more important to realize that the effects of intervention can be defined only in human populations. What are the effects of early treatment of motor or mental deficits or the prevention of repeated seizures? Only studies of well-defined populations of children who suffer from these disorders may answer these questions. As we indicated, every attempt has to be made to restrict variables and to attempt to define a relatively homogeneous population, but we must accept the fact that we will never find a group of identical children all having exactly the same background and the same handicap. All research concerning the treatment of developmental disabilities over time will require techniques for defining, ordering and manipulating one or more primary and multiple secondary variables. This means that the future study of the treatment of developmental disabilities will become increasingly dependent upon progress in fundamental research in biostatistics.

We have reached a point where we are beginning to translate some of our knowledge of the development of the normal human brain into the treatment of the brain damaged child. Diet, use of chemical co-factors to correct metabolic disorders, early childhood training programs and programs to prevent the causes of developmental disabilities are burgeoning. These disorders are chronic problems that are especially stressful to parents who, in their frustration and their love for their children, often seek any source of help that offers some hope or the possibility of cure. Past experience shows, however, that this is not a field where there are going to be many remarkable *break throughs.* Reliable, controlled investigation to define causes, to treat them, and to prove the value of a specific therapy in reducing the consequences of a specific symptom or sign is the kind of research that is needed. Given patience and determination, the slow but steady program of the medical, psychological and educational communities will win this race.

References

1. Myklebust, H.R. Identification and diagnosis of children with learning disabilities. An interdisciplinary study of criteria. In S. Walzer & P. Wolff (Eds.), *Minimal brain dysfunction.* New York, NY: Grune and Stratton, 1973. Pp. 55-77.
2. Nelson, K.B., & Ellenberg, J.H. Epidemiology of cerebral palsy. In B.S. Schoenberg (Ed.), *Neurological epidemiology: Principles and clinical application.* New York, NY: Raven Press, 1978. Pp. 421-435.
3. Lemkau, P., Tietze, C., & Cooper, M. Mental hygiene problems in an urban district. *Mental Hygiene,* 1942, 26, 275.
4. Rutter, M. The development of infantile autism. *Psychological Medicine,* 1971, 4, 147.
5. Bax, M.C.O. Terminology and classification of cerebral palsy. *Developmental Medicine and Child Neurology,* 1964, 6, 295.
6. Durkin, M.V., Kraveggia, E.G., Pendleton, E., Neuhauser, G., & Optiz, J.M. Analysis of etiologic factors in cerebral palsy with severe mental retardation: Analysis of gestational, parturitional and neonatal data. *European Journal of Pediatrics,* 1976, 123, 67.
7. Banker, B.Q., & Larroche, J-C. Periventricular leukomalacia of infancy: A form of neonatal hypoxia. *Archives of Neurology,* 1962, 7, 386.

8. Takashima, S., & Tanaka, K. Development of cerebrovascular architecture and its relationship to periventricular leukomalacia. *Archives of Neurology,* 1978, 35, 11.
9. McManus, F., Raug, M., Chance, G., & Whittaker, J. Is cerebral palsy a preventable disease? *Obstetrics and Gynecology,* 1977, 50, 71.
10. Advanced cardiac life support for neonates. In, Standards for cardiopulmonary resuscitation and emergency cardiac care. *JAMA,* 1980, 244, 495.
11. Brown, J.K., Purvis, R.J., Forfar, J.O., & Cockburn, F. Neurological aspects of perinatal asphyxia. *Developmental Medicine and Child Neurology,* 1974, 16, 567.
12. Nelson, K.B., & Ellenberg, J.H. Neonatal signs as predictors of cerebral palsy. *Pediatrics,* 1979, 64, 225.
13. Land, P.W., & Lund, R.D. Development of the rat's uncrossed retinotectal pathway and its relation to plasticity studies. *Science,* 1979, 202, 698.
14. Goldman, P.S. Neuronal plasticity in primate telencephalon: Anomalous projections induced by prenatal removal of frontal cortex. *Science,* 1978, 202, 768.
15. Evarts, E.V. Activity of cerebral neurons in relation to movement. In D.B. Tower (Ed.), *The nervous system: Volume I: The basic neurosciences.* New York, NY: Raven Press, 1975. P. 221.
16. Bobath, B. The very early treatment of cerebral palsy. *Developmental Medicine and Child Neurology,* 1967, 9, 373.
17. Sellick, K.J., & Over, R. Effects of vestibular stimulation on motor development of cerebral-palsied children. *Developmental Medicine and Child Neurology,* 1980, 22, 476.
18. Young, R.R., & Delwaide, P.J. Spasticity. *New England Journal of Medicine,* 1981, 304, 28, 96.
19. Penn, R.D., Myklebust, B.M., Gottlieb, G.L., Agarwal, G.C., & Etzel, M.E. Chronic cerebellar stimulation for cerebral palsy: Prospective and double blind studies. *Journal of Neurosurgery,* 1980, 53, 160.
20. Gray, M.Z. (Ed.). *Mental retardation: Past and present.* Report of the President's Committee on Mental Retardation. Washington, DC: U.S. Government Printing Office, 1977. P. 143.
21. Buist, N.R.M., & Jhaveri, B.M. A guide to screening newborn infants for inborn errors of metabolism. *Journal of Pediatrics,* 1973, 82, 511.
22. Brady, R.O. Enzymalogical approaches to the lipidoses. *Annals of Clinical Laboratory Science,* 1977, 7, 105.
23. Sly, W.S. The mucopolysaccharidoses. In P.K. Bondy & L.E. Rosenberg (Eds.), *Metabolic control and disease.* Philadelphia, PA: W.B. Saunders Co., 1980. P. 545.
24. Johnson, G.B. Enzyme polymorphism and metabolism: Polymorphism among enzyme loci as related to metabolic function. *Science,* 1974, 164, 28.
25. Jacobs, P.A., Matsuura, J.S., Mayer, M., & Newlands, I.M. A cytogenetic survey of an institution for the mentally retarded: I. Chromosome abnormalities. *Clinical Genetics,* 1978, 13, 37.
26. Turner, G., Brookwell, R., Daniel, A., Selikowitz, M., & Zilibowitz, M. Heterozygous expression of x-linked mental retardation and x-chromosome marker fra (X) (q27). *New England Journal of Medicine,* 1980, 303, 662.

27. LaFranchi, S.H., Murphey, W.H., Foley, T.P., Jr., Larsen, P.H., & Buist, N.R.M. Neonatal hypothyroidism detected by the Northwest Regional Screening Program. *Pediatrics,* 1979, 63, 180.
28. Epstein, C.J., & Globus, M.S. The prenatal diagnosis of genetic disorders. *Amer. Rev. Med.,* 1978, 29, 117.
29. Burton, B.K., & Nadler, H.L. Clinical diagnosis of the inborn errors of metabolism in the neonatal period. *Pediatrics,* 1978, 61, 398.
30. Johnson, R.T. Selective vulnerability of neural cells to viral infections. *Brain,* 1980, 103, 447.
31. Purpura, D.P. Dendritic spine "dysgenesis" and mental retardation. *Science,* 1974, 186, 1126.
32. Committee on Nutrition of the American Academy of Pediatrics. Special diets for infants with inborn errors of amino acid metabolism. *Pediatrics,* 1976, 57, 783.
33. Rosenberg, L.E. Vitamin-responsive inherited metabolic disorders. In H. Harris & K. Hirschhorn (Eds.), *Advances in human genetics* (Volume VI). New York, NY: Plenum Publishing Corporation, 1976. P. 1.
34. Bickel, H., Schmidt, H., & Schierrle, L. Dietary treatment of inborn errors of amino acid and carbohydrate metabolism. *Bibliotheca Nutritio et Dieta,* 1973, 18, 181.
35. Krasner, L., & Ullmann, L.P. *Behavior, influence and personality: The social matrix of human action.* New York, NY: Holt, Rinehart and Winston, Inc., 1973. P. 560.
36. Friedman, S.L., & Sigman, M. (Eds.). *Preterm birth and psychological development.* New York, NY: Academic Press, 1981. P. 425.
37. Cantwell, D.P. *The hyperactive child: Diagnosis, management and current research.* New York, NY: Spectrum Publications, 1975. P. 209.
38. Needleman, H.L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C., & Barrett, P. Deficits in psychological and classroom performance of children with elevated dentine lead levels. *New England Journal of Medicine,* 1979, 300, 689.
39. Mountcastle, V.B. Brain mechanisms for directed attention. *Journal of the Royal Society of Medicine,* 1978, 71, 14.
40. Barchas, J.D., Akil, H., Elliott, G.R., Holman, R.B., & Watson, S.J. Behavioral neurochemistry: Neuroregulators and behavioral states. *Science,* 1978, 200, 964.
41. Weiss, G., & Hechtman, L. The hyperactive child syndrome. *Science,* 1979, 205, 1348.
42. Rodier, P.M. Critical periods for behavioral anomalies in mice. *Environmental Health Perspectives,* 1976, 18, 79.
43. Martin, J.T. Imprinting behavior: Pituitary-adrenocortical modulation of the approach response. *Science,* 1978, 200, 565.
44. Whalen, C.K., Henker, B., & Dotemoto, S. Methylphenidate and hyperactivity: Effects on teacher behaviors. *Science,* 1980, 208, 1280.
45. Williams, J.I., Cram, D.M., Tausig, F.T., & Webster, E. Relative effects of drugs and diet on hyperactive behaviors: An experimental study. *Pediatrics,* 1978, 61, 811.
46. Harley, J.P., Matthews, C.G., & Eichman, P. Synthetic food colors and hyperactivity in children: A double-blind challenge experiment. *Pediatrics,* 1978, 62, 975.

47. Rutter, M., & Bartak, L. Some causes of infantile autism: Some considerations from recent research. *Journal of Autism and Childhood Schizophrenia,* 1971, 1, 20.
48. Hier, D.E., LeMay, M., & Rosenberger, P.B. Autism: Association with reversed cerebral asymmetry. *Neurology,* 1978, 28, 348. (Abstract)
49. Lockman, L.A., Swaiman, K.F., Drage, J.S., Nelson, K.B., & Marsden, H.M. *Workshop on the neurobiological basis of autism.* Washington, DC: National Institutes of Health. NIH Publication No. 79-1855, 1979. P. 297.
50. Ornitz, E.M. Childhood autism: A review of the clinical and experimental literature. *California Medicine,* 1973, 118, 21.
51. Cohen, D.J., Caparulo, B.K., Johnson, W.T., & Bowers, M.B. Biogenic amines in autistic and atypical children: Cerebrospinal fluid measures of homovanillic and 5-hydroxyindoleacetic acid. *Archives of General Psychiatry,* 1974, 31, 845.
52. Rimland, B., Callaway, E., & Dreyfus, P. The effect of high doses of vitamin B_6 on autistic children: A double-blind crossover study. *American Journal of Psychiatry,* 1978, 135, 472.
53. Gastaut, H. Clinical and electroencephalographical classification of epileptic seizures. *Epilepsia,* 1970, 11, 102.
54. Hauser, W.A. Epidemiology of epilepsy. In B.S. Schoenberg (Ed.), *Advances in neurology* (Volume 19). New York, NY: Raven Press, 1978. P. 313.
55. Rose, S.W., Penry, J.K., Markush, R.E., Radloff, L.A., & Putnam, P.L. Prevalence of epilepsy in children. *Epilepsia,* 1973, 14, 133.
56. Alter, M., & Hauser, W.A. (Eds.). *The epidemiology of epilepsy: A workshop.* Washington, DC: National Institute of Neurological and Communicative Disorders and Stroke, DHEW Publication No. (NIH) 73-390, 1972. P. 167.
57. Merlis, J.K. Epilepsy in different age groups. In M. Alter & W.A. Hauser (Eds.), *The epidemiology of epilepsy: A workshop.* Washington, DC: National Institute of Neurological and Communicative Disorders and Stroke, DHEW Publication No. (NIH) 73-390, 1972. Pp. 83-86.
58. Nelson, K.B., & Ellenberg, J.H. Prognosis in children with febrile seizures. *Pediatrics,* 1978, 61, 720.
59. Holowach, J., Thurston, D.L., & O'Leary, J. Prognosis in childhood epilepsy. *New England Journal of Medicine,* 1972, 286, 169.
60. Emerson, R., D'Souza, B.J., Vining, E.P., Holden, K.R., Mellits, E.D., & Freeman, J.M. Stopping medication in children with epilepsy. *New England Journal of Medicine,* 1981, 304, 1125.
61. Ferrendelli, J.A., & Kinscherf, D.A. Cyclic nucleotides in epileptic brain: Effects of pentylenetetrazol on regional cyclic AMP and cyclic GMP levels *in vivo. Epilepsia,* 1977, 18, 525.
62. Collins, R.C. Metabolic response to focal penicillin seizures in rat: Spike discharge vs. afterdischarge. *Journal of Neurochemistry,* 1976, 27, 1473.
63. Collins, R.C., & Ferrendelli, J.A. Neurochemistry of epileptic discharge. In S.G. Eliasson, A.L. Prensky, & W.B. Hardin, Jr. (Eds.), *Neurological pathophysiology* (2nd Ed.). New York, NY: Oxford University Press, 1978. Pp. 196-198.
64. Ferrendelli, J.A. Epilepsy and cyclic nucleotides. In P. Hamet & H. Sands (Eds.), *Advances in cyclic nucleotide research* (Volume 12). New York, NY: Raven Press, 1980. Pp. 199-211.

65. Savaki, H.E., Davidsen, L., Smith, C., & Sokoloff, L. Measurement of free glucose turnover in brain. *Journal of Neurochemistry,* 1980, 35, 495.
66. Duffy, T.E., Howse, D.C., & Plum, F. Cerebral energy metabolism during experimental status epilepticus. *Journal of Neurochemistry,* 1975, 24, 925.
67. Kuhl, D.E., Engel, J., Jr., Phelps, M.E., & Selin, C. Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of ^{18}FDG and $^{13}NH_3$. *Annals of Neurology,* 1979, 8, 348.
68. Beresford, H.R., Posner, J.B., & Plum, F. Changes in brain lactate during induced cerebral seizures. *Archives of Neurology,* 1969, 20, 243.
69. Wasterlain, C.G. Developmental effects of seizures: Role of malnutrition. *Pediatrics,* 1976, 57, 197.
70. Knopman, D., Margolis, G., & Reeves, A.G. Prolonged focal epilepsy and hypoxemia as a cause of focal brain damage: A case study. *Annals of Neurology,* 1977, 1, 195.
71. Goldring, S. Pathophysiology of epileptic discharge. In S.G. Eliasson, A.L. Prensky, & W.B. Hardin (Eds.), *Neurological pathophysiology* (2nd Ed.). New York, NY: Oxford University Press, 1978. Pp. 183-195.
72. Penry, J.K., Porter, R.J., & Dreifuss, F.E. Simultaneous recording of absence seizures with video tape and electroencephalography. *Brain,* 1975, 98, 427.
73. Sutula, T.P., Sackellares, J.C., Miller, J.Q., & Dreifuss, F.E. Intensive monitoring in refractory epilepsy. *Neurology,* 1981, 31, 243.
74. Holmes, G.L., Sackellares, J.C., McKiernan, J., Ragland, M., & Dreifuss, F.E. Evaluation of childhood pseudoseizures using EEG telemetry and video tape monitoring. *Journal of Pediatrics,* 1980, 97, 554.
75. Yang, P.J., Berger, P.E., Cohen, M.E., & Duffner, P.K. Computed tomography and childhood seizure disorders. *Neurology,* 1979, 29, 1084.
76. Oakley, J., Ojemann, G.A., Ojemann, L.M., & Cromwell, L. Identifying epileptic foci on contrast-enhanced computerized tomographic scans. *Archives of Neurology,* 1979, 36, 669.
77. Glaser, G.H., Penry, J.K., & Woodbury, D.M. (Eds.). *Antiepileptic drugs: Mechanisms of action.* New York, NY: Raven Press, 1980. P. 728.
78. Dodson, W.E. The nonlinear kinetics of phenytoin in children. *Neurology,* in press.
79. Montouris, G.D., Fenichel, G.M., & McLain, L.W., Jr. The pregnant epileptic. *Archives of Neurology,* 1979, 36, 601.
80. Huttenlocher, P.R. Ketonemia and seizures: Metabolic and anticonvulsant effects of two ketogenic diets in childhood epilepsy. *Pediatric Research,* 1976, 10, 536.
81. Spencer, S.S. Depth electroencephalography in selection of refractory epilepsy for surgery. *Annals of Neurology,* 1980, 9, 207.
82. Goldring, S. A method for surgical management of focal epilepsy, especially as it relates to children. *Journal of Neurosurgery,* 1978, 49, 344.
83. VanBuren, J.M., Wood, J.H., Oakley, J., & Hambrecht, F. Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. *Journal of Neurosurgery,* 1978, 48, 407.
84. Levy, L.F., & Auchterlonie, W.C. Chronic cerebellar stimulation in the treatment of epilepsy. *Epilepsia,* 1979, 20, 235.

85. Wilson, D.H., Reeves, A., & Gazzaniga, M. Division of the corpus callosum for uncontrollable epilepsy. *Neurology*, 1978, 28, 649.
86. Wasterlain, C.G. Effects of epileptic seizures on brain ribosomes: Mechanism and relationship to cerebral energy metabolism. *Journal of Neurochemistry*, 1977, 29, 707.
87. Freedman, R., Taylor, D.A., Seiger, A., Olson, L., & Hoffer, B.J. Seizures and related epileptiform activity in hippocampus transplanted to the anterior chamber of the eye: Modulation by cholinergic and adrenergic input. *Annals of Neurology*, 1979, 6, 281.
88. Aguilar, M.J., & Rasmussen, T. Role of encephalitis in pathogenesis of epilepsy. *Archives of Neurology*, 1960, 2, 663.
89. Kurokawa, T., Goya, N., Fukuyama, Y., Suzuki, M., Seki, T., & Ohtahara, S. West syndrome and Lennox-Gastaut syndrome: A survey of natural history. *Pediatrics*, 1980, 65, 81.
90. Crowther, D.L. Psychosocial aspects of epilepsy. *Pediatric Clinics of North America*, 1967, 14, 921.
91. Freeman, J.M., & Gayle, E. Rehabilitation and the client with epilepsy: A survey of the client's view of the rehabilitation process and its results. *Epilepsia*, 1978, 19, 233.